IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.      : 10/583,364
Applicant      : Joseph Zawierucha et al
Filed          : June 19, 2006
TC/A.U.        : 1616
Examiner       : Danielle D. Sullivan

Docket No.    : 3165-147
Customer No. : 6449
Confirmation No.: 8196

## RESPONSE TO ELECTION OF SPECIES REQUIREMENT

Commissioner for Patents
P.O. Box 1450                                             September 30, 2008
Alexandria, VA 22313-1450

Dear Sir:

In response to the Election of Species Requirement dated September 3, 2008, the

applicants hereby elect for herbicide B carfentrazone and for herbicide A imazapyr.

The Examiner took the position that the herbicides A and B lack the same or

corresponding special technical feature, but this comment is not understood in the

context of an election of species requirement. In any event, claim 1 is directed to a

method of controlling coniferous plants by contacting the plants with herbicide B. Claim

2 is directed to controlling coniferous plants by applying to the coniferous plants that

have been or are to be contacted with herbicide B a further herbicide A. That is, the

present application does not have claims relating to the application of herbicide A to

coniferous plants or plant parts that are not also contacted by herbicide B. The

present invention is based on the finding that carfentrazone and sulfentrazone

are particularly suitable for controlling coniferous plants. Both carfentrazone
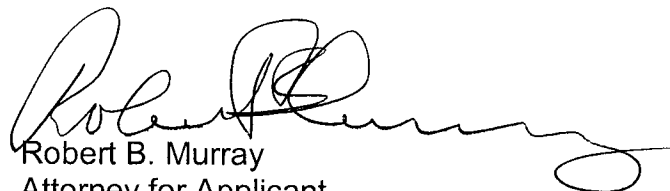
and sulfentrazone share a common mode of action in that they are both inhibitors of protoporphyrinogen-IX-oxydase (so called protox inhibitors). In contrast to other protox inhibitors based on phenyl substituted heterocyles, they share a close structural similarity in that both are 2-(substituted)phenyl-4-difluoromethyl-5-methyl-1,2,4-triazolinones (see page 158 of "Modern Crop Protection Compounds, Volume 1, Wiley-VCH Verlag GmbH & Co. KG, Weinheim 2007, copy enclosed). Thus, sulfentrazone and carfentrazone have a corresponding technical feature and their use in a method for controlling coniferous plants forms a single general inventive concept under PCT rule 13.1.

Claims 1-6, 13-22, 25-26, 31-32 and 34-35 read on the elected species.

Early and favorable action on the merits is awaited.

Respectfully submitted,

By

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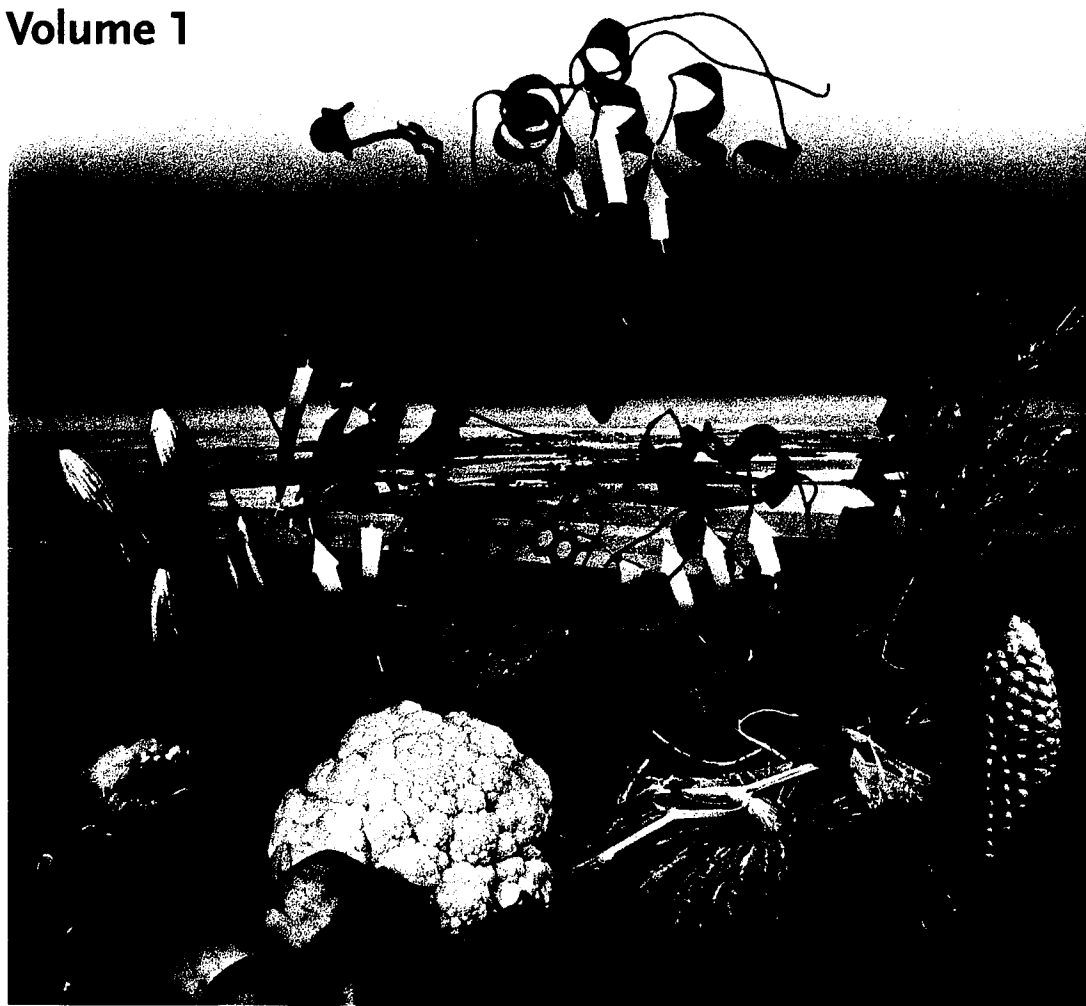Edited by Wolfgang Krämer
and Ulrich Schirmer

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# Modern Crop
# Protection Compounds

Volume 1

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# 3

# Protoporphyrinogen-IX-oxidase Inhibitors

*George Theodoridis*

## 3.1
## Introduction

Rarely do we encounter an area of agrochemical research with both the chemical diversity and the very specific and often conflicting structure–activity relationship (SAR) rules as is the case with the herbicidal protoporphyrinogen oxidase (Protox) inhibitors. It was this incredible array of possibilities that lured every single agrochemical organization during the 1980s and 1990s in the United States, Europe, and Asia into initiating a research effort, in the hope of finding the next blockbuster herbicide. Soon, many Protox areas that were initially seen as having unlimited potential turned into dead ends, with only a handful of commercial products achieving significant market share. Part of the difficulty in exploiting the Protox area of herbicide chemistry was the fact that even though it was relatively easy to find chemistries with good biological activity, it was much harder to find clear crop selectivity, either on pre-emergently or post-emergently applied materials.

The lack of clear selectivity of several commercially significant row crops was overcome following the discovery of several highly active and selective Protox herbicides such as the post-emergence soybean selective herbicide fomesafen **7** (Flex®, Flexstar®, Reflex®) [1, 2], introduced in 1983 by ICI Plant Protection Division, and the soybean selective pre-emergence herbicides F5231, compound **14** [3–5], and sulfentrazone (**15**) (Authority®, Boral®, Capaz®) [6–8] introduced by FMC in 1991.

Research in Protox herbicides peaked in the early 1990s [9] and diminished soon after as the use of glyphosate-resistant crops gained increased market share. Glyphosate, N-(phosphonomethyl)glycine, is a broad-spectrum, post-emergence, systemic herbicide that has been used extensively over the past 30 years. This intense and prolonged use of glyphosate has resulted in documented resistance to glyphosate in several weed populations [10], which, in turn, has stimulated new interest in Protox-inhibiting herbicides.

The mode of action of Protox herbicides has been extensively reviewed [11–17]. Protox herbicides act by inhibition of the enzyme protoporphyrinogen oxidase, the last common enzyme to both heme and chlorophyll biosynthesis [18–23]. The protoporphyrinogen oxidase enzyme catalyzes the oxidation of protoporphyrinogen IX to protoporphyrin IX by molecular oxygen. Inhibition of the Protox enzyme results in the accumulation of the enzyme product protoporphyrin IX, but not the substrate, via a complex process that has not been entirely elucidated. In the presence of light, protoporphyrin IX generates large amounts of singlet oxygen, which results in the peroxidation of the unsaturated bonds of fatty acids found in cell membranes (Fig. 3.1). The end result of this peroxidation process is the loss of membrane integrity and leakage, pigment breakdown, and necrosis of the leaf that results in the death of the plant. This is a relatively fast process, with leaf symptoms such as a flaccid wet appearance observed within hours of plant exposure to the Protox herbicide under sunlight.

In this chapter, we discuss recent developments and challenges in the field of Protox-inhibiting agrochemicals and place those agrochemicals in the context of research done in this area of chemistry in the past four to five decades.

## 3.2
## Historical Development

The diphenyl ether nitrofen (1) [24], introduced in 1963 by Rohm and Haas, now Dow AgroSciences; the oxadiazolinone oxadiazon (2) [25, 26] (Explorer®, Herbstar®, Romax®, Ronstar®), introduced in 1968 by Rhone-Poulenc; and the tetrahydrophthalimide chlorophthalim 3 [27], introduced in 1972 by Mitsubishi, represent the earliest examples of Protox herbicides (Fig. 3.2). Though all three classes are chemically quite different, they share a common mode of action, inhibition of the protoporphyrinogen oxidase enzyme, though this was not known until the late 1980s.

Each of these chemistries generated intensive work in the 1960s–1980s, which resulted in numerous diverse chemistries, from which several useful commercial products were obtained.

### 3.2.1
### Diphenyl Ether

Following the discovery of the herbicidal activity of nitrofen (1) in 1963, intense research by several agrochemical companies resulted in a vast number of highly active and diverse chemistries [28, 29]. As mentioned earlier, the diphenyl ether chemistry represents the first class of Protox herbicides. Replacement of the aromatic 4-chloro group with a trifluoromethyl, as is the case with oxyfluorfen (5) (Goal®) [30], resulted in a significant improvement in biological activity, and 2-
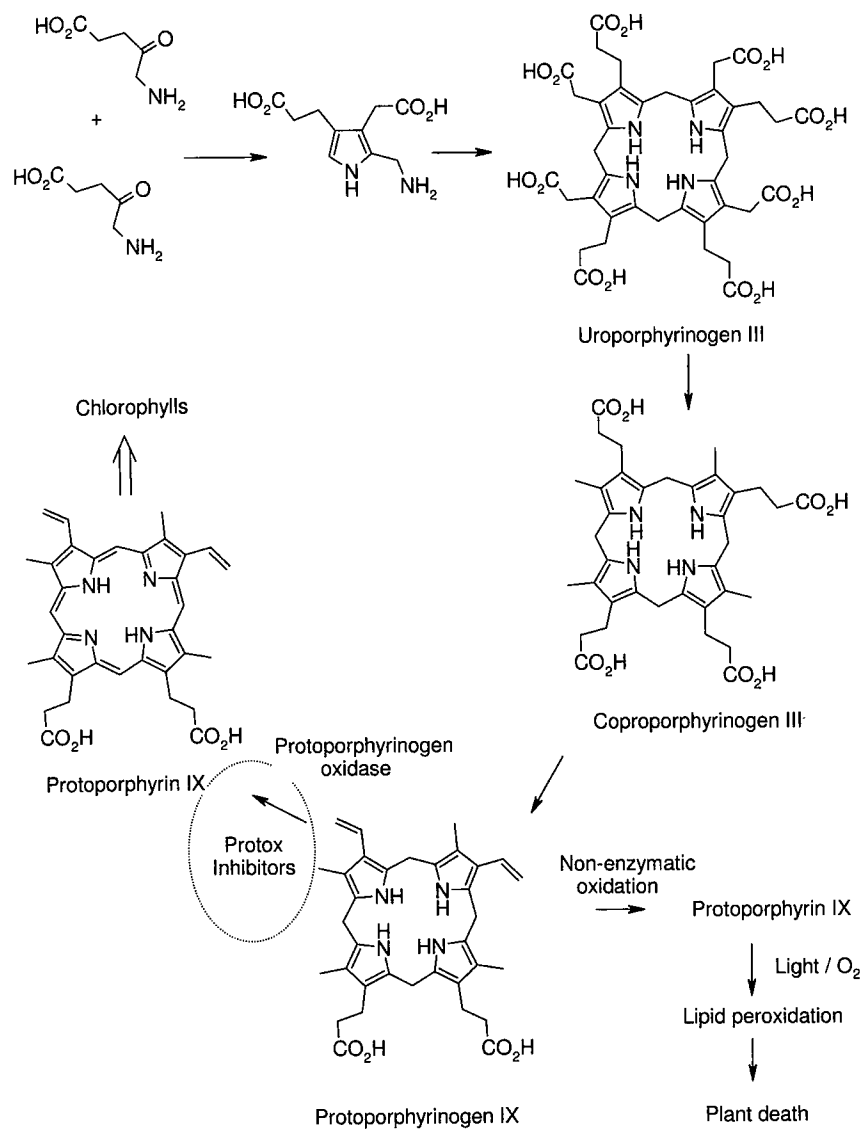
**Fig. 3.1.** Chlorophyll biosynthetic pathway.

chloro-4-(trifluoromethyl)benzene became the dominant substitution pattern for the second generation of diphenyl ethers (Fig. 3.3), eventually replacing products such as nitrofen (1) and bifenox (4) (Foxpro®, Modown®) [31]. As can be seen from Fig. 3.3, the 2-chloro-1-(3-substituted-4-nitrophenoxy)-4-(trifluoromethyl)-benzene became the most successful diphenyl ether chemistry scaffold, with four
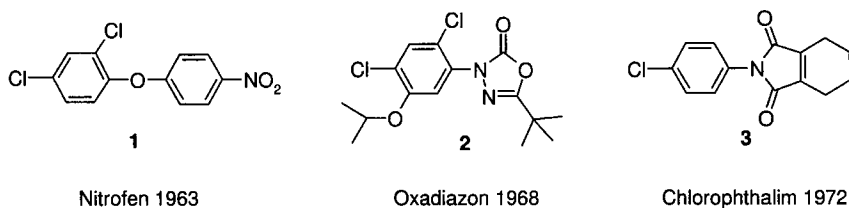
Nitrofen 1963    Oxadiazon 1968    Chlorophthalim 1972

**Fig. 3.2.** Chemical structures of three early examples of Protox inhibitors.

significant products launched in fewer than ten years. In general, diphenyl ether herbicides such as oxyfluorfen (5) (Goal®), acifluorfen-sodium (6) (Blazer®) [32, 33], fomesafen (7) (Flex®, Flexstar®, Reflex®) [1, 2], and lactofen (8) (Cobra®) [34] are more effective when applied post-emergently, and are more effective for the control of broadleaf than of grass weeds.

Though the 1980s and early 1990s were a period of intense research in diphenyl ether chemistry, the main products described above were all introduced by 1987. By 1996, sales of diphenyl ethers had peaked at $381 million, steadily declining to $200 million by 2001 [35]. This decline was due to the introduction of more effective herbicides, as well as the increasing adoption of herbicide-tolerant crops. Despite this decline, research in diphenyl ether chemistry continued, resulting in the third generation of diphenyl ethers. This newer group of diphenyl ether herbicides consisted of compounds in which either the nitrophenyl ring was replaced by various fused benzoheterocycles, such as benzotriazole [36], benzoisoxazole [37], and indolin-2(3H)-ones [38], or the 2-chloro-4-(trifluoromethyl)benzene group was replaced by a heterocyclic ring such as pyrazole [39].

The extensive research invested by many companies in this third generation of diphenyl ether chemistry resulted in many active molecules, but no successful commercial product.



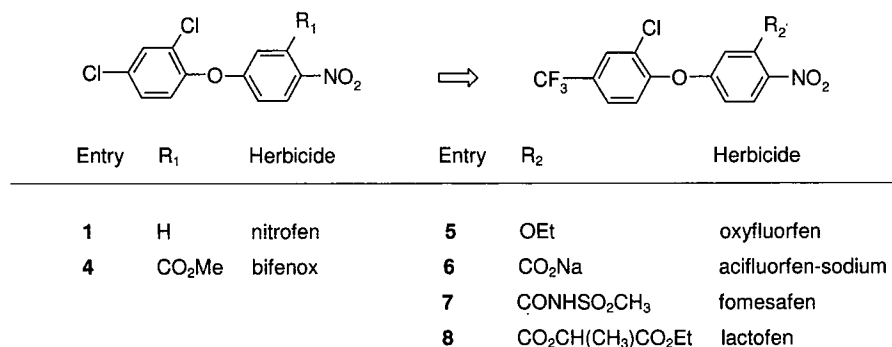| Entry | R₁ | Herbicide | Entry | R₂ | Herbicide |
|-------|------|-----------|-------|----------------|--------------------|
| 1 | H | nitrofen | 5 | OEt | oxyfluorfen |
| 4 | CO₂Me | bifenox | 6 | CO₂Na | acifluorfen-sodium |
| | | | 7 | CONHSO₂CH₃ | fomesafen |
| | | | 8 | CO₂CH(CH₃)CO₂Et | lactofen |

**Fig. 3.3.** Evolution of diphenyl ether herbicides.

### 3.2.2
### Phenyl Ring Attached to Heterocycle

Several discoveries made in the 1960s had a significant impact on our understanding of the structure–activity of Protox herbicides. The first breakthrough was the discovery of the importance of the 2,4-dihalo-5-substituted-phenyl substitution pattern. Rhone-Poulenc first introduced 3-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2($3H$)-one (**9**) in 1965 [40]. Further structure–activity optimization at the phenyl ring soon led to the discovery in 1968 of the 2,4-dichloro-5-isopropoxyphenyl substitution pattern of the herbicide oxadiazon (**2**) [41, 42]. The 2,4-dihalo-5-substituted pattern at the aromatic ring would become the basis for much of the 2,4,5-trisubstituted phenyl tetrahydrophthalimide **10** [43] research that followed in the Protox area of chemistry.

Another breakthrough discovery was the boost in biological activity caused by the replacement of chlorine by fluorine at the 2-phenyl position. In 1976, DuPont introduced the first example of a 2-fluoro-4-chlorophenyl tetrahydrophthalimide Protox inhibitor (**11**) [44] (Fig. 3.4). The dramatic increase in biological activity caused by the fluorine in the 2 position of the phenyl ring would, in the next decade, the 1980s, influence work in the Protox area, such as the discovery of the 4-chloro-2-fluorophenyltetrahydrophthalimide herbicide S-23142 (**12**) [45].

The herbicide oxadiazon (**2**) is used for the pre-emergence control of annual broadleaf weeds and grasses and bindweed, and for the post-emergence control of annual broadleaf weeds in ornamentals such as carnations and roses, as well as in fruit trees, vines, cotton, rice, and turf. It requires high application rates of 1 kg-a.i. ha$^{-1}$ for weed control in rice, and up to 4 kg-a.i. ha$^{-1}$ for pre-emergence weed control in vines and orchards [25, 26]. The high rates of pre-emergence application, the limited selectivity in several row crops, and the introduction of
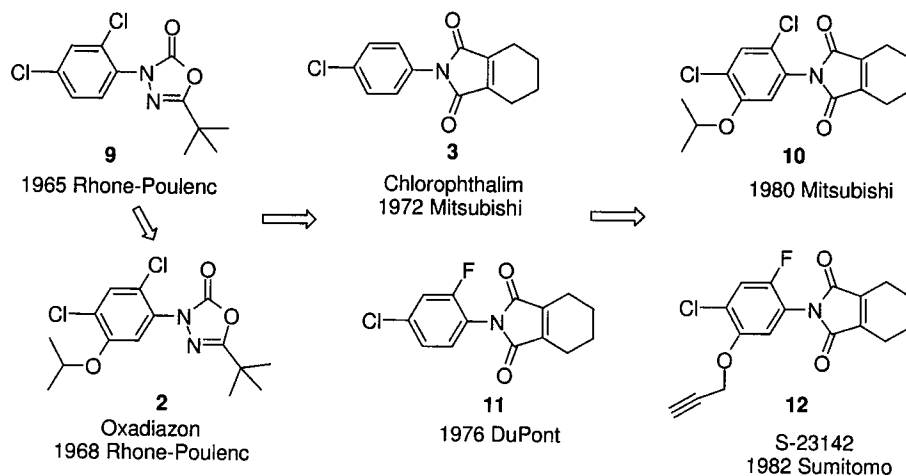


**9**
1965 Rhone-Poulenc

Chlorophthalim
1972 Mitsubishi
**3**

**10**
1980 Mitsubishi

**2**
Oxadiazon
1968 Rhone-Poulenc

**11**
1976 DuPont

**12**
S-23142
1982 Sumitomo

**Fig. 3.4.** Incorporation of the 2,4-dihalo-5-alkoxy aromatic pattern of oxadiazon into new phenyl tetrahydrophthalimide ring systems.
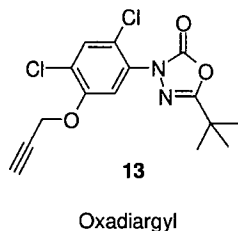
Oxadiargyl

**Fig. 3.5.** Chemical structure of oxadiargyl (**13**).

newer, more effective herbicides all have served to limit the commercial use of oxadiazon (**2**). Later, Rhone-Poulenc introduced oxadiargyl (**13**) (Raft®, Topstar®) [46, 47] (Fig. 3.5), a compound related to oxadiazon, for the control of broadleaf weeds, grass, and annual sedge in transplanted rice.

In the 1980s, several chemical changes on the 1,3,4-oxadiazol-2(3H)-one heterocyclic system resulted in several significant improvements in the pre- and post-emergence biological efficacy and crop selectivity of Protox herbicides. Detailed discussion of the various classes of phenyl heterocycles introduced several decades ago is beyond the scope of this chapter; they have been previously reviewed [28]. The introduction in 1985 of the 5-aminosulfonyl group in the phenyl ring of 2,4,5-trisubstituted-phenyl tetrazolinones was one such significant change. F5231 (**14**) [5], a molecule under development consideration by FMC in the late 1980s, was the first Protox inhibitor to provide excellent pre-emergence broadleaf control and clear selectivity at low application rates on several crops such as soybean, rice, corn, and wheat. FMC later replaced F5231 (**14**) with the phenyl triazolinone sulfentrazone (**15**) for soybean, sugarcane, and other crops [6–8]. Sulfentrazone (**15**) provides pre-emergence control of several broadleaf weeds – as well as several selected grass weeds – for the soybean market. A few years later, FMC introduced a second commercial phenyl triazolinone, the post-emergence cereal and corn herbicide carfentrazone-ethyl (**16**) (Aim®, Affinity®, Aurora®) [48, 49]. At low rates of 20–35 g-a.i. ha$^{-1}$ carfentrazone-ethyl (**16**) provides excellent control of weeds in commercially important cereal crops – weeds such as bedstraw, speedwell, morning-glory, kochia, spurge, and deadnettle [50] (Fig. 3.6).
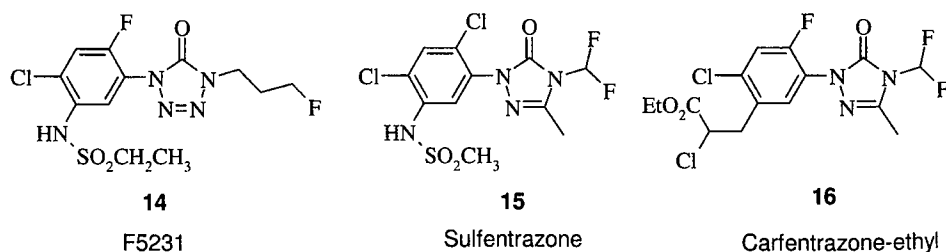


| **14** | **15** | **16** |
|---|---|---|
| F5231 | Sulfentrazone | Carfentrazone-ethyl |

**Fig. 3.6.** Chemical structure of F5231 (**14**), sulfentrazone (**15**), and carfentrazone-ethyl (**16**).

**17**

Fluazolate

**18**

Pyraflufen-ethyl

**19**
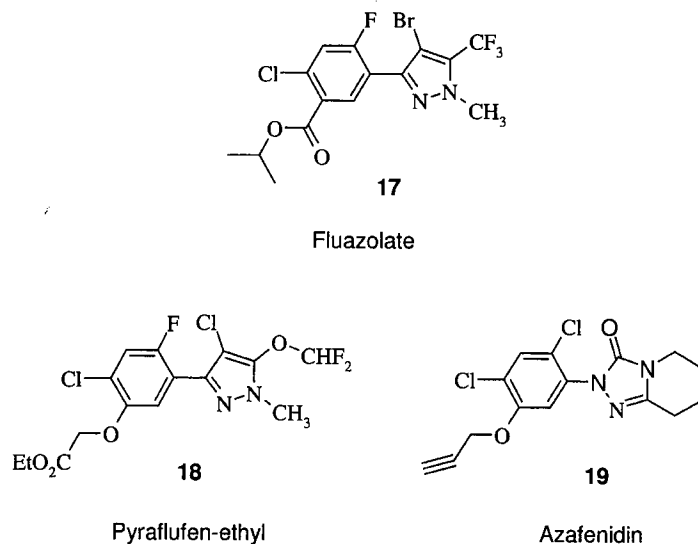
Azafenidin

**Fig. 3.7.** Chemical structure of fluazolate (**17**), pyraflufen-ethyl (**18**), and azafenidin (**19**).

In addition to the oxadiazolinone, tetrazolinone, and triazolinone heterocyclic ring systems, other five-membered ring systems investigated in the 1980s included pyrazoles, such as fluazolate (**17**) [51] from Monsanto; pyraflufen-ethyl (**18**) (Ecopart®) [52, 53], introduced in 1993 by Nihon Noyaku as a post-emergence broadleaf herbicide in cereals; and fused triazolinone rings such as azafenidin (**19**) [54, 55] from DuPont (Fig. 3.7).

## 3.2.3
### Phenyl Tetrahydrophthalimide

Phenyl tetrahydrophthalimides represent the third class of early Protox herbicides. They were introduced in the early 1970s, after the diphenyl ether and 1,3,4-oxadiazol-2(3H)-one chemistries. Following the introduction by Mitsubishi of chlorophthalim (**3**) [27] in 1972, incorporation of the 2,4,5-trisubstituted-phenyl pattern in the 1980s resulted in the synthesis of highly active molecules such as S-23142 (**12**) [45], and S-23121 (**20**) [45, 56] (Fig. 3.8).

The tetrahydrophthalimide area of chemistry generated a great deal of interest between 1980 and 2000, with hundreds of patents issued by a wide range of agro-chemical companies [29]. Once the fluorine group at the 2-phenyl position and the chlorine group at the 4-phenyl position were established as the optimum substituents for the aromatic ring, the 5 position of the phenyl ring and the tetrahydrophthalimide heterocycle became the target of intense research. A wide variety of oxygen (**21**), sulfur (**22**), amino (**23**), and carbonyl (**24**) derivatives at the 5 posi-